Claims

1. A method for making a water insoluble biocompatible composition, said method comprising combining, in an aqueous mixture, a polyanionic polysaccharide, a nucleophile, and an activating agent under conditions sufficient to form said composition.

2. The method of claim 1 wherein two or more polyanionic polysaccharides are employed.

3. The method of claim 1 or 2 wherein said polyanionic polysaccharides are chosen from the group consisting of carboxymethyl cellulose, carboxymethyl amylose, hyaluronic acid, chondroitin-6-sulfate, dermatin sulfate, heparin, and heparin sulfate.

4. The method of claim 1 wherein said polyanionic polysaccharide is hyaluronic acid.

5. The method of claim 1 wherein said polyanionic polysaccharide is carboxymethyl cellulose.

6. The method of claim 1 wherein said polyanionic polysaccharide is carboxymethyl amylose.

7. The method of claim 2 wherein two of said polyanionic polysaccharides are hyaluronic acid and carboxymethyl cellulose.

8. The method of claim 1 wherein said activating agent is chosen from the group consisting of benzotriazole-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, *O*-benzotriazole-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium

hexafluorophosphate, bromotris(dimethylamino)phosphonium hexafluorophosphate, bromotris(pyrrolidinyl)phosphonium hexafluorophosphate and the corresponding halide salts thereof.

9. The method of claim 1 wherein said polyanionic polysaccharide are present in a concentration of 0.0002 - 0.1M.

10. The method of claim 9 wherein said polyanionic polysaccharide is present in a concentration of 0.0005 - 0.02M.

11. The method of claim 1 wherein said method is carried out at a pH 3.5 - 8.0.

12. The method of claim 1 wherein the stoichiometry of said activating agent to said polysaccharide is at least 0.1 molar equivalent of said activating agent per molar equivalent of said polyanionic polysaccharide.

13. The method of claim 1 wherein said nucleophile is chosen from the group consisting of an amino acid amide, a monofunctional amine, an amino acid ester, an amino alcohol, an amino thiol, an amino phenol, an amino catechol, an amino acid, a salt of an amino acid, a peptide, and a protein.

14. The method of claim 1 wherein the stoichiometry of said polyanionic polysaccharide to said nucleophile is at least 1 molar equivalent of nucleophile per molar equivalent of polyanionic polysaccharide.

15. A method for making a water insoluble biocompatible composition, said method comprising combining, in an aqueous mixture, one or more polyanionic polysaccharides, a modifying compound, a nucleophile, and an activating agent under conditions sufficient to form said composition wherein said modifying compound causes the formation of a new active carbonyl groups on said polyanionic polysaccharide.

16. The method of claim 15 wherein two or more polyanionic polysaccharides are employed.

17. The method of claim 15 or 16 wherein said polyanionic polysaccharides are chosen from the group consisting of carboxymethyl cellulose, carboxymethyl amylose, hyaluronic acid, chondroitin-6-sulfate, dermatin sulfate, heparin, and heparin sulfate.

18. The method of claim 15 wherein said polyanionic polysaccharide is hyaluronic acid.

19. The method of claim 15 wherein said polyanionic polysaccharide is carboxymethyl cellulose.

20. The method of claim 15 wherein said polyanionic polysaccharide is carboxymethyl amylose.

21. The method of claim 16 wherein two of said polyanionic polysaccharides are hyaluronic acid and carboxyl methyl cellulose.

22. The method of claim 15 wherein said modifying compound is chosen from the group consisting of

1-hydroxybenzotriazole hydrate, 1-hydroxybenzotriazole monohydrate, N-hydroxysulfosuccinimide, N-hydroxysuccinimide, 4-nitrophenol, 2-nitrophenol, 4-nitrothiophenol, 2-nitrothiophenol, pentachlorophenol, pentafluorophenol, imidazole, tetrazole, and 4-dimethylaminopyridine.

23. The method of claim 15 wherein said activating agent comprises a carbodiimide.

24. The method of claim 23 wherein said carbodiimide comprises 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide methiodide.

25. The method of claim 15 wherein said polyanionic polysaccharide is present in a concentration of 0.0002 - 0.1M.

26. The method of claim 25 wherein said polyanionic polysaccharide is present in a concentration of 0.0005 to 0.02M.

27. The method of claim 15 wherein said method is carried out at a pH 3.5 - 8.0.

28. The method of claim 15 wherein the stoichiometry of said polyanionic polysaccharide to said activating agent is at least 0.1 molar equivalent of said activating agent per molar equivalent of said polyanionic polysaccharide.

29. The method of claim 15 wherein the stoichiometry of said modifying agent to said activating agent is at least 1 molar equivalent of said modifying compound per molar equivalent of said activating agent.

30. The method of claim 15 wherein said nucleophile is chosen from the group consisting of an amino acid amide, a monofunctional amine, an amino acid ester, an amino alcohol, an amino thiol, an amino phenol, an amino catechol, an amino acid, a salt of an amino acid, a peptide, and a protein.

31. A water insoluble composition prepared according to the method of claim 1, 2, 15 or 16.

32. The composition of claim 31 wherein said composition is in the form of a gel.

33. The composition of claim 31 wherein said composition is in the form of fibers.

34. The composition of claim 31 wherein said composition is in the form of a membrane.

35. The composition of claim 31 wherein said composition is in the form of a foam.

36. The composition of claim 31 wherein said composition is in the form of an adhesion prevention composition.

37. The composition of claim 31, further comprising a pharmaceutically active substance dispersed within said composition.

38. The composition of claim 37 wherein said pharmaceutically active substance is chosen from the group consisting of proteins, growth factors, enzymes, drugs, biopolymers, and biologically compatible synthetic polymers.

39. A water insoluble composition comprising the reaction product of a polyanionic polysaccharide, a nucleophile, and an activating agent.

40. A water insoluble composition comprising the reaction product of two or more polyanionic polysaccharides, a nucleophile, and an activating agent.

41. The water insoluble composition of claim 39 or 40 wherein said activating agent is chosen from the group consisting of benzotriazole-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate, *O*-benzotriazole-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, bromotris(dimethylamino)phosphonium hexafluorophosphate, bromotris(pyrrolidinyl)phosphonium hexafluorophosphate and the corresponding halide salts thereof.

42. A water insoluble composition comprising the reaction product of a polyanionic polysaccharide, a modifying compound, a nucleophile, and an activating agent.

43. A water insoluble composition comprising the reaction or product of two or more polyanionic polysaccharides, a modiying compound, a nucleophile, and an activating agent.

44. The composition of claim 39, 40, 42 or 43 wherein said polyanionic polysaccharides are chosen from the group consisting of carboxymethyl cellulose, carboxymethyl amylose, hyaluronic acid, chondroitin-6-sulfate, dermatin sulfate, heparin, and heparin sulfate.

45. The composition of claim 39 or 42 wherein said polyanionic polysaccharide is hyaluronic acid.

46. The composition of claim 39 or 42 wherein said polyanionic polysaccharide is carboxymethyl cellulose.

47. The composition of claim 39 or 42 wherein said polyanionic polysaccharide is carboxymethyl amylose.

48. The composition of claim 40 or 43 wherein two of said polyanionic polysaccharides are hyaluronic acid and carboxy methyl cellulose.

49. The composition of claim 39, 40, 42 or 43 wherein said nucleophile is chosen from the group consisting of an amino acid amide, a monofunctional amine, an amino acid ester, an amino alcohol, an amino thiol, an amino phenol, an amino catechol, an amino acid, a salt of an amino acid, a peptide, and a protein.

50. The composition of claim 42 or 43 wherein said modifying compound is chosen from the group consisting of 1-hydroxybenzotriazole hydrate, 1-hydroxybenzotriazole monohydrate, N-hydroxysulfosuccinimide, N-hydroxysuccinimide, 4-nitrophenol, 2-nitrophenol,

4-nitrothiophenol, 2-nitrothiophenol, pentachlorophenol, pentafluorophenol, imidazole, tetrazole, and 4-dimethylaminopyridine.

51. The composition of claim 42 or 43 wherein said activating agent comprises a carbodiimide.

52. The composition of claim 51 wherein said carbodiimide comprises 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide methiodide.

53. The composition of claims 39, 40, 42 or 43 wherein said composition is in the form of a gel.

54. The composition of claims 39, 40, 42 or 43 wherein said composition is in the form of fibers.

55. The composition of claims 39, 40, 42 or 43 wherein said composition is in the form of a membrane.

56. The composition of claims 39, 40, 42 or 43 wherein said composition is in the form of a foam.

57. The composition of claims 39, 40, 42 or 43 wherein said composition is in the form of an adhesion prevention composition.

58. The composition of claims 39, 40, 42 or 43, further comprising a pharmaceutically active substance dispersed within said composition.

59. The composition of claim 58 wherein said pharmaceutically active substance is chosen from the group consisting of proteins, growth factors, enzymes, drugs, biopolymers, and biologically compatible synthetic polymers.